

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

-----X	:	
SANOFI-SYNTHELABO;	:	
SANOFI-SYNTHELABO, INC.; and	:	02 Civ. 2255 (SHS)
BRISTOL-MYERS SQUIBB SANOFI	:	
PHARMACEUTICALS	:	
HOLDING PARTNERSHIP,	:	
	:	<u>OPINION</u>
Plaintiffs,	:	
	:	
-against-	:	
	:	
APOTEX INC.; and APOTEX CORP.,	:	
	:	
Defendants.	:	
-----X		

SIDNEY H. STEIN, U.S. District Judge.

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## I. OVERVIEW

Plavix, the most widely prescribed prescription blood-thinning agent in the world, prevents platelets in blood from aggregating around obstructions—such as metal stents or cholesterol deposits—in arterial passageways. Forty-eight million Americans take Plavix daily to prevent potentially fatal blood clots. This action arose between Sanofi-Aventis, Sanofi-Synthelabo, Inc. and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (collectively, “Sanofi”)—those entities that invested in the research and development to patent this drug and bring it to market—on the one hand, and Apotex, Inc. and Apotex Corporation (collectively, “Apotex”)—which seeks to market the generic equivalent of Plavix—on the other. Before the Court is a motion by Sanofi to preliminarily enjoin Apotex from distributing its generic version of Plavix in the United States after an at-risk launch of that drug by Apotex approximately three weeks ago, on August 8, 2006. Sanofi seeks to enjoin Apotex from any further distribution of the generic drug pending an ultimate decision on the merits of this action and has also requested that the Court order a recall of the product already distributed.

In this action, the parties have agreed and stipulated that Apotex’s generic product in fact infringes Sanofi’s patent. Apotex does not dispute that but rather claims that

Sanofi's patent is invalid and unenforceable. Because Sanofi has adequately demonstrated that the questions Apotex raises as to the validity and enforceability of Sanofi's '265 patent are without substantial merit based on the evidence adduced to date, Sanofi has demonstrated a likelihood of success on the merits at trial. Further, Sanofi will suffer irreparable harm due to Apotex's continued distribution of the infringing pharmaceutical, and Apotex's hardships primarily arise from the company's own calculated risk-taking. Finally, although there are competing—and substantial—public interests at stake on both sides of this litigation, the balance of those competing public interests slightly favors Sanofi. For these reasons, and because the Court finds Apotex's laches and unclean hands defenses to be without merit, Sanofi's motion is granted insofar as Apotex is enjoined from further distribution of its generic product. Sanofi's motion is denied insofar as it requests a recall of the product Apotex has already distributed.

## **II. BACKGROUND**

In the context of the Court's consideration of a motion for a preliminary injunction, "all findings of fact and conclusions of law . . . are subject to change upon the ultimate trial on the merits." Purdue Pharma L.P. v. Boehringer Ingelheim GmbH, 237 F.3d 1359, 1363 (Fed. Cir. 2001) (citing Illinois Tool Works, Inc. v. Grip-Pak, Inc., 906 F.2d 679, 681 (Fed. Cir. 1990)); University of Texas v. Camenisch, 451 U.S. 390, 395, 101 S. Ct. 1830, 1834, 68 L. Ed. 2d 175 (1981)). The Court finds the following facts for the purposes of this Opinion.

### **A. History of this Action**

Plavix, approved for sale in the United States by the U.S. Food and Drug Administration (“FDA”) in November 1997, is prescribed for the reduction of thrombotic events, such as heart attacks and strokes, for patients who have recently suffered such events or who have arterial disease or acute coronary syndrome. (See Stipulated Statement of Facts (“Fact Stmt”), attached as Ex. A to Joint Pretrial Order dated May 27, 2005 at ¶ 12.) The active ingredient of Plavix is clopidogrel bisulfate. (Id.) Sanofi obtained a patent claiming clopidogrel bisulfate on July 11, 1989, naming Sanofi employees Alain Badorc and Daniel Fréhel as inventors. (Id. at ¶¶ 8-9.) That patent, U.S. patent number 4,847,265 (“the ‘265 patent”), claims clopidogrel bisulfate by its chemical name in claim three: “hydrogen sulfate of the dextro-rotatory isomer of methyl alpha 5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl)(2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.” (Id. at ¶¶ 9-10.) The ‘265 patent is exclusively licensed to the Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership and expires on November 17, 2011. (Id. at ¶ 9.)

Apotex sought approval from the FDA to manufacture and sell clopidogrel bisulfate tablets before the expiration of Sanofi’s ‘265 patent by filing an Abbreviated New Drug Application (“ANDA”) with the FDA in November 2001. (Fact Stmt at ¶¶ 14-15.) In the ANDA, Apotex certified that it believed the ‘265 patent to be invalid, pursuant to the requirements of 21 U.S.C. § 355(j)(2)(vii)(IV). (Id. at ¶ 16; see Glaxo Group Ltd. v. Apotex, Inc., 376 F.3d 1339, 1344 (Fed. Cir. 2004) (pursuant to 21 U.S.C. § 355(j)(2)(A)(I)-(IV), a generic company has an obligation to “certify that either (I) no patent information is listed . . . for the proposed generic drug; (II) that the listed patents have expired; (III) that the listed patents will expire before the generic company markets

its product; or (IV) that the patents listed are invalid or will not be infringed by the generic drug.”.) Apotex was the first to file an ANDA for clopidogrel bisulfate (Decl. of Dr. Bernard Sherman, dated Aug. 16, 2006 (“Sherman Decl.”) at ¶ 17), thereby securing the right to 180 days of market exclusivity provided by the Hatch-Waxman Act to the first ANDA filer to challenge a patent. See 21 U.S.C. § 355(j)(5)(B)(iv); see also In re Tamoxifen Citrate Antitrust Litig., 429 F.3d 370, 376 (2d Cir. 2005).

In response to that ANDA filing by Apotex, Sanofi filed this suit against Apotex on March 21, 2002 pursuant to 35 U.S.C. § 271(e), on the ground that Apotex’s filing of the ANDA constituted infringement of the ‘265 patent. Section 271(e)(2)(A) provides that “it shall be an act of infringement to submit (A) an application . . . for a drug claimed in a patent or the use of which is claimed in such a patent, . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale” of the drug before the expiration of the patent. See also Glaxo Group, 376 F.3d at 1344 (“Section 271(e)(2)(A) provides a jurisdictional basis for a declaratory judgment suit against a generic manufacturer.”); Glaxo, Inc. v. Novopharm Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997) (“§ 271(e)(2) provided patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity.”).

Apotex counterclaimed, asserting that the ‘265 patent is invalid for three reasons. First, because it was anticipated by the prior art—specifically by Sanofi’s own prior patent, the ‘596 patent—pursuant to 35 U.S.C. § 102(b). Second, because the subject matter claimed in the patent would have been obvious to a person of ordinary skill in the art at the time the invention was made, pursuant to 35 U.S.C. § 103. Third, because it

was invalid under the judicial doctrine of obviousness-type double patenting. (See Third Amended Answer and Amended Counterclaim (“Answer”), filed Jan. 14, 2005.) Apotex also asserts that the ‘265 patent is unenforceable on the basis of Sanofi’s alleged inequitable conduct before the U.S. Patent and Trademark Office (“PTO”) in that Sanofi failed to name Dr. Jean-Pierre Maffrand as an inventor, made false statements to the PTO regarding the unexpected pharmacological properties of clopidogrel bisulfate, failed to disclose relevant prior research that Sanofi had conducted on a similar chemical compound, and failed to disclose a journal article Apotex alleges is a material prior art reference. (See id.)

This action was originally supervised by Judge Robert W. Sweet and was transferred to this Court in February of 2004. By a Stipulation and Order endorsed by this Court on May 7, 2004, the parties agreed that Apotex’s clopidogrel bisulfate product infringes claim 3 of Sanofi’s ‘265 patent. (See May 7, 2004 Stipulation and Order.) Thus, a major issue in many patent litigations—whether or not the generic product infringes the patent holder’s patent—is not in contention here, but rather is agreed upon. The parties then pursued a lengthy course of discovery and motions, all leading to the entry of a final pretrial order in July 2005. The matter was set down for a March 2006 trial.

#### **B. Events Giving Rise to This Motion**

According to provisions of the Hatch-Waxman Act, 21 U.S.C. § 355(j)(5)(B)(iii), Sanofi’s filing of a patent infringement suit against Apotex triggered an automatic stay barring the FDA from approving Apotex’s ANDA for thirty months. (See Sherman Decl.

at ¶ 18.) The stay expired on May 17, 2005 and the FDA approved Apotex's ANDA eight months later, on January 20, 2006. (Sherman Decl. at ¶¶ 19, 24.)

Anticipating the expiration of the 30-month stay of FDA approval of its ANDA, Apotex informed Sanofi in October 2005 that it expected final approval by the FDA to be "imminent." (Sherman Decl. at ¶ 21; Letter by Robert Silver to Robert Baechtold dated Oct. 24, 2005, attached as Ex. A to Sherman Decl.) In the October 2005 letter, Apotex informed Sanofi that it intended to launch its product as soon as possible after FDA approval and asserted that "it cannot be appropriate for Plaintiffs to do nothing until launch is imminent and only then bring a motion for an injunction." (*Id.*) On January 20, 2006 the FDA gave final approval to Apotex's ANDA. (Sherman Decl. at ¶ 24.)

Several days before the FDA announced its final approval of Apotex's ANDA, Sanofi and Apotex began discussions in an attempt to resolve this litigation. (*See* Decl. of Robert L. Baechtold dated Aug. 20, 2006 ("Baechtold Decl.") at ¶ 2.) On the same afternoon that the FDA approved Apotex's ANDA, an email from Apotex's counsel to Sanofi's counsel memorialized "the terms of the settlement we reached." (*See* Jan. 16, 2006 Email, attached as Ex. 1 to Baechtold Decl.) This "settlement" provided that "during settlement negotiations Apotex will not launch its generic product and Sanofi will not launch an authorized generic and will not move for an injunction." (*Id.*) An email several days later from Sanofi's counsel to Apotex's counsel included the "final version of the agreements between our[] clients as reflected in our exchange of emails" and attached an agreement that also stipulated that Apotex would not launch its generic and Sanofi would not move for an injunction during settlement negotiations. (Jan. 20, 2006 email, attached as Ex. 2 to Baechtold Decl.) Thus, the parties agreed in January of

2006 that neither party would launch a generic, nor would Sanofi move for a preliminary injunction while settlement discussions were ongoing.

Although the trial had initially been set for March 2006, Apotex requested that the trial be delayed because Apotex's counsel had another trial scheduled to begin in early March. (Baechtold Decl. at ¶ 5.) The parties then entered into a second agreement, on February 8, 2006, providing that Apotex would seek a postponement of the trial for three months to accommodate its own counsel's trial schedule, and that Sanofi would consent to the postponement. (Baechtold Decl. at ¶¶ 6-7; Feb. 8, 2006 Agreement, attached as Ex. 3 to Baechtold Decl.) The parties again agreed that neither party would launch a generic product and Sanofi would not move for a temporary restraining order or preliminary injunction during that period of postponement. (*Id.*) The parties then requested an adjournment of the trial date for three months. That request was granted and the trial was rescheduled for June 2006.

Six weeks later—on St. Patrick's Day, March 17, 2006—the parties reached an agreement to resolve the litigation. (Sherman Decl. at ¶ 32; Baechtold Decl. at ¶ 8; March 17, 2006 Agreement, attached as Ex. 4 to Baechtold Decl.) The agreement was subject to approval by the FTC and a consortium of state attorneys general under an order entered in a previous litigation involving Bristol-Myers Squibb. (Sherman Decl. at ¶ 32.) The parties submitted the agreement for the required regulatory review, but the state attorneys general informed the parties in early May that they would not approve the settlement as written. (Sherman Decl. at ¶ 34.)

After the March 17 agreement was rejected, the parties negotiated a second. (Sherman Decl. at ¶ 35; Baechtold Decl. at ¶ 9; May 26, 2006 Agreement (“Second



Agreement”), attached as Ex. 5 to Baechtold Decl.) This second agreement, dated May 26, 2006, was also submitted for regulatory approval; however on July 28, 2006 the state attorneys general informed Sanofi’s counsel that the “states object to and will not approve the Settlement Agreement.” (Sherman Decl. at ¶ 47; July 28, 2006 Letter, attached as Ex. E to Sherman Decl.) Paragraph 13 of the Second Agreement provides that “if Regulatory Review has not been completed by July 31, 2006 either party has the right to declare that there has been regulatory denial.” (Second Agreement at ¶ 13.) In a letter dated July 31, 2006, Apotex declared regulatory denial. (Baechtold Decl. at ¶ 10.)

The Second Agreement contains a number of terms that were to enter into force in the event of regulatory denial. (See Second Agreement at ¶¶ 14-15.) Paragraph 14 provides, in relevant part, that in the event of regulatory denial, the litigation between the parties will resume “as further described in paragraph 15” and that Sanofi agrees that:

if the litigation results in a judgment that the ‘265 patent is not invalid or unenforceable, Sanofi agrees that its actual damages for any past infringement by Apotex, up to the date on which Apotex is enjoined, will be 50% of Apotex’s net sales of clopidogrel products if Sanofi has not launched an authorized generic . . . . Sanofi further agrees that it will not seek increased damages under 35 U.S.C. § 284.

Paragraph 15 provides that if the regulatory review results in regulatory denial, the parties agree that:

- (i) Until 5 business days after the date on which Regulatory Denial is effective (not counting the day on which it becomes effective), Apotex will not launch a generic clopidogrel bisulfate product and Sanofi will not launch an authorized generic product, and Sanofi will not seek a temporary restraining order or a preliminary injunction.
- (ii) After the expiration of the period defined in sub-paragraph (i), Sanofi agrees that it will not launch an authorized generic clopidogrel product before a launch by Apotex of a generic clopidogrel product, and Sanofi will not, at any time, file for a temporary restraining order, and will not file for a preliminary

injunction until Sanofi gives Apotex 5 business days notice . . . of its intention to do so, which notice will not be given before Apotex has initiated a launch of a generic clopidogrel product.

Immediately after Apotex declared regulatory denial on Monday July 31, 2006, Sanofi sought a temporary restraining order barring Apotex from launching its generic clopidogrel bisulfate product. The Court denied that motion on Friday, August 4, 2006, on the ground that Sanofi had explicitly agreed not to seek a temporary restraining order in Paragraph 15 of the Second Agreement and had not provided any tangible evidence that Apotex was in material breach of the agreement. (See Tr. of Aug. 4, 2006 hearing.)

On Tuesday, August 8, 2006, approximately one week after declaring regulatory denial, Apotex launched its generic clopidogrel bisulfate product. Sanofi notified Apotex on that same day that it intended to move for a preliminary injunction in the time frame set forth in paragraph 15 of the Second Agreement, which permitted Sanofi to file for a preliminary injunction five business days after the launch by Apotex of its generic product. Sanofi thus moved for a preliminary injunction on Tuesday, August 15, 2006. Apotex filed responsive papers including affidavits and reports by several fact and expert witnesses, and the Court heard testimony during a hearing conducted on August 18 and 21, 2006.

### **III. PRELIMINARY INJUNCTION**

#### **A. Legal Standard**

On substantive questions of patent law, this Court is bound by the precedents of the U.S. Court of Appeals for the Federal Circuit. See Hybritech, Inc. v. Abbott Labs., 849 F.2d 1446, 1451 n.12 (Fed. Cir. 1988). The decision whether to grant or deny a preliminary injunction in the context of a patent dispute pursuant to 35 U.S.C. § 283 is

committed to the discretion of the Court. See Polymer Techs. v. Bridwell, 103 F.3d 970, 973 (Fed. Cir. 1996); Novo Nordisk of North Am., Inc. v. Genentech, Inc., 77 F.3d 1364, 1367 (Fed. Cir. 1996). In addition, all findings of fact and conclusions of law at the preliminary injunction stage are subject to change upon the ultimate trial on the merits. See Illinois Tool Works, 906 F.2d at 681 (citing Camenisch, 451 U.S. at 395).

As the moving party, Sanofi carries the burden of demonstrating the propriety of a preliminary injunction, “in light of the following four factors: (1) a reasonable likelihood of success on the merits; (2) irreparable harm if the injunction were not granted; (3) the balance of the hardships and (4) the impact of the injunction on the public interest.” Polymer Techs., 103 F.3d at 973. “Analysis of each of the four factors is generally appropriate ‘for reasons of judicial economy and . . . appellate review,’” but with two exceptions. Id. (quoting Reebok Int’l Ltd. v. J. Baker, Inc., 32 F.3d 1552, 1557 (Fed. Cir. 1994)). First, if the moving party “clearly establishes the first factor (by making a ‘clear showing’ of both validity and infringement), it [is] entitled to a rebuttable presumption” of irreparable harm. Id. (citing Smith Int’l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1581 (Fed. Cir. 1983)). Second, “if the moving party fails to establish either of the first two factors,” then “a trial court need not make findings concerning the third and fourth factors” before proceeding to deny the preliminary injunction. Id. (quoting Reebok, 32 F.3d at 1556).

## **B. Likelihood of Success**

In order to demonstrate that it has a likelihood of success, Sanofi must show that, “in light of the presumptions and burdens that will inhere at trial on the merits, (1) it will likely prove . . . [infringement] and (2) its infringement claim will likely withstand

[Apotex's] challenges to the validity and enforceability of the . . . patent.” Genentech, Inc., 108 F.3d at 1364; see also Canon Computer Sys., Inc. v. Nu-Kote Int'l, Inc., 134 F.3d 1085, 1088 (Fed. Cir. 1998) (citing Nutrition 21, 930 F.2d at 869-70). In this context, the patent is accorded an initial presumption of validity and enforceability pursuant to 35 U.S.C. § 282. See New England Braiding Co. v. A.W. Chesterton Co., 970 F.2d 878, 882 (Fed. Cir. 1992) (citation omitted). If, however, Apotex produces evidence raising a “‘substantial question’ concerning validity, enforceability, or infringement,” then Sanofi must produce countervailing evidence demonstrating that these defenses “‘lack[] substantial merit.’” Genentech, Inc., 108 F.3d at 1364 (citation omitted).

In its opposition to the preliminary injunction motion, Apotex admits its product infringes Sanofi's patent, but raises three defenses: First, Apotex argues that the '265 patent is invalid because it was anticipated by an earlier Sanofi patent, the '596 patent. Second, Apotex argues that the '265 patent is invalid for obviousness because it would have been obvious to a person of ordinary skill in the art based on that earlier Sanofi patent and other prior art in the field. Third, Apotex asserts that the '265 patent is unenforceable because of inequitable conduct committed by Sanofi during the prosecution of the application for the '265 patent at the PTO. Ultimately, Apotex will bear the burden at trial of proving each of these defenses by clear and convincing evidence. See Oney v. Ratliff, 182 F.3d 893, 895 (Fed. Cir. 1999) (invalidity); Elk Corp. v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir.) (unenforceability), cert. denied, 145 L. Ed. 2d 150, 120 S. Ct. 178 (1999). At the preliminary injunction stage,

however, the Court considers primarily whether the defenses asserted by Apotex raise a substantial question regarding the validity and enforceability of the ‘265 Patent.

### **1. Infringement**

As noted above, Apotex admits and stipulates that the generic clopidogrel bisulfate product that is the subject of its ANDA infringes claim 3 of Sanofi’s ‘265 patent, which claims “[h]ydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thieno pyridyl) (2-chlorophenyl)-acetate,” also known as clopidogrel bisulfate. (See Fact Stmt at ¶¶ 18-19; May 7, 2004 Stipulation and Order.)

### **2. Invalidity**

“A patent shall be presumed valid,” and “[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.” 35 U.S.C. § 282. To overcome this presumption of validity at trial, “the party challenging a patent must prove facts supporting a determination of invalidity by clear and convincing evidence.” Schumer v. Lab. Computer Sys., 308 F.3d 1304, 1315 (Fed. Cir. 2002) (citing Apotex USA, Inc. v. Merck & Co., 254 F.3d 1031, 1036, (Fed. Cir. 2001), cert. denied, 534 U.S. 1172, 122 S. Ct. 1196, 152 L. Ed. 2d 136 (2002)). At the preliminary injunction stage, however, “the trial court does not resolve the validity question but rather must . . . make an assessment of the persuasiveness of the challenger’s evidence, recognizing that it is doing so without all evidence that may come out at trial.” New England Braiding Co., 970 F.2d at 883. The Court finds Apotex’s evidence insufficiently persuasive to establish a likelihood of proving invalidity at trial.

### a. Anticipation

#### *i. Legal Standards*

Pursuant to 35 U.S.C. § 102, an invention may receive a patent only if it is ‘novel’ in relation to the ‘prior art’ available to the public at the time the patent application is filed. See 35 U.S.C. § 102(b). A prior art reference renders a patented invention “anticipated—and thus invalid—if it “discloses every feature of the claimed invention, either explicitly or inherently.” Hazani v. United States ITC, 126 F.3d 1473, 1477 (Fed. Cir. 1997); see also Schering Corp. v. Geneva Pharms., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003) (“[A] prior art reference which expressly or inherently contains each and every limitation of the claimed subject matter anticipates and invalidates.”) (citations omitted).

To disclose the features of the claimed invention, the prior art must “describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation.” Advanced Display Sys., Inc. v. Kent State Univ., 212 F. 3d 1272, 1282 (Fed. Cir. 2000); see also Mehl/Biophile Int’l Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999). The disclosure must therefore be “an enabling disclosure,” rather than merely “vague intimations of general ideas that may or may not be workable.” Genentech, Inc., 108 F.3d at 1366 (citing Brenner v. Manson, 383 U.S. 519, 536, 16 L. Ed. 2d 69, 86 S. Ct. 1033 (1966)).

Apotex alleges that the ‘265 patent is anticipated by an earlier patent Sanofi held that covered a genus of chemical compounds called thienopyridines, within which clopidogrel bisulfate falls. This earlier patent, U.S. Patent No. 4,529,596 (“the ‘596 patent”) issued in July 1985, four years before the ‘265 patent issued, and expired in July

2003. (See Fact Stmt at ¶ 28.) Indeed, the parties have stipulated that clopidogrel bisulfate is “a compound that is within the genus of claim one of the ‘596 patent.” (*Id.* at ¶ 32.) Apotex asserts that this prior patent fully disclosed and thus anticipates clopidogrel bisulfate; Sanofi defends the novelty of the ‘265 patent on the ground that the ‘596 patent was not an enabling disclosure. In other words, it did not “describe every element” of clopidogrel bisulfate “such that a person of ordinary skill in the art could practice the invention without undue experimentation.” *Advanced Display Sys.*, 212 F.3d at 1282. To address this issue, some technical background is necessary.

*ii. The ‘596 and ‘265 Patents*

The ‘596 patent is entitled “Thieno [3,2-c] Pyridine Derivatives and Their Therapeutic Application,” and describes a genus of compounds that exhibit blood-platelet aggregation inhibition and anti-thrombotic activity. (Fact Stmt at ¶ 27; ‘596 patent at col. 8, lines 22-24.) The thienopyridines described in the ‘596 patent are all racemic compounds. (Testimony of Dr. Jean-Pierre Maffrand, Transcript of Preliminary Injunction Hearing dated Aug. 18 & 21, 2006 (“tr.”), at 136-137; Affidavit of Dr. Robert Snyder dated Jun. 8, 2004 at 3.) A racemic compound is chiral, meaning that it has an asymmetric carbon, or “chiral,” center. (*Id.*) A chiral center is composed of a carbon atom connected to four other atoms—in the case of the compounds described in the ‘596 patent, the carbon atom is connected to a nitrogen atom, a hydrogen atom and two other carbon atoms. (Maffrand, tr. at 136-37.) A racemic mixture, also known as a racemate, is a mixture of molecules with asymmetric carbon centers. The racemate consists of an equal number of each of two enantiomers. (Expert Report of Dr. Stephen G. Davies dated July 6, 2004, attached as Ex. 1 to Decl. of Stephen G. Davies dated Aug. 11, 2006,

at ¶ 32.) The two enantiomers are two different spatial configurations of the same molecule. (Id. at ¶¶ 27-29.) The enantiomers are non-superimposable mirror images of each other, such as a right and a left hand. (Id. at ¶ 27.) The two enantiomers generally have identical physical properties—such as melting at the same temperature and dissolving in solvents to the same extent—except for one characteristic: If a chemist directs a plane of polarized light through a solution of just one of the two enantiomers, the enantiomer will rotate the light to the right or to the left. (Id. at ¶ 30, 41.) If an enantiomer rotates light to the right, it is described as “dextrorotatory,” while if the enantiomer rotates light to the left it is described as “levorotatory.” (Id. at ¶ 30.) When the name for a chemical compound with an asymmetric carbon center does not indicate a particular enantiomer, a chemist will understand the compound to be a racemate; that is, a mixture that contains an equal number of dextro- and levo- rotatory enantiomers. (Id. at ¶ 32.)

The ‘596 patent discloses a group of compounds described by a general formula. Because the formula has two variables (X and Y), each of which can be one of a number of enumerated substituents, with 37 possibilities for the X variable and 1710 possible choices for Y, the general formula covers an extremely large number compounds.<sup>1</sup> (Davies at ¶¶ 60-64; Expert Report of Dr. Stephen R. Byrn dated July 9, 2004, attached as Ex. 1 to Decl. of Stephen R. Byrn dated Aug. 11, 2006, at ¶¶ 55-58; Maffrand, tr. at 137.) Each of the described compounds is racemic (Maffrand, tr. at 137); however the

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<sup>1</sup> Multiplying these variables by the number of pharmaceutically acceptable salts yields an even higher number. Maffrand testified that “if we mix and match all the claimed substituents . . . and if we take into account the different salts which can be made for each of these compounds,” the ‘596 patent covers “millions” of compounds, each of which would have a chiral center and be racemic. (Maffrand, tr. at 137.) Sanofi’s expert Dr. Stephen Davies, basing his calculations on 50 pharmaceutically acceptable salts, estimates the number to be “almost 9.5 million different compounds.” (Davies at ¶¶ 63-64.)



‘596 patent states that “[t]he invention relates both to each enantiomer and their mixture.” (‘596 patent col. 1, lines 40-41; Maffrand, tr. at 140.)

A chemist charged with finding a suitable form for a drug compound transforms it into a solid form by adding an acid or base to form a crystalline salt. (Byrn at ¶¶ 15, 28.) The ‘596 patent sets forth that the thienopyridine compounds within the genus claimed by the patent can be made into addition salts with pharmaceutically acceptable mineral or organic acids or a mineral base. (Byrn at ¶ 57; ‘596 patent, col. 1, lines 42-51.)

The ‘596 patent gives 21 examples of particular compounds included within the genus compound “to exemplify and to illustrate the different substituents which were claimed in the general formula.” (Maffrand, tr. at 138; see Snyder at 14.) These different compounds are described in the patent as different salts forms—particularly, hydrobromide, hydrochloride and bisulfate salts. (Maffrand, tr. at 139-140.) The first of the 21 examples in the ‘596 patent is a thienopyridine racemate entitled “methyl alpha-5(4,5,6,7-tetrahydro (3,2-c) thienopyridyl)(2-chlorophenyl) acetate.” (‘596 patent col. 3, lines 37-41; Snyder at 3.) Sanofi referred to this compound internally as “PCR 4099.” (Maffrand, tr. at 138.) PCR 4099 was described in the ‘596 patent as a hydrochloride salt. (Maffrand, tr. at 139.)

The later patent, that is, the ‘265 patent which is at issue here, claims the “[h]ydrogen sulfate of the dextro-rotatory enantiomer of methyl alpha-5(4,5,6,7-tetrahydro (3,2-c) thienopyridyl)(2-chlorophenyl) acetate.” (Fact Stmt at ¶¶ 18, 19.) In other words, the ‘265 patent claims the dextrorotatory enantiomer of the racemate PCR 4099, which has been given the generic name “clopidogrel,” (Snyder at 18), prepared as a bisulfate salt.

### *iii. Apotex's Case for Anticipation*

Apotex asserts that the later '265 patent is anticipated by the earlier '596 patent because, it urges, the earlier '596 patent both describes clopidogrel bisulfate and enables a person of ordinary skill in the art to produce it. In Apotex's view, the '596 patent describes clopidogrel bisulfate by claiming the class of thienopyridines to which clopidogrel belongs, by stating that the patent covers the thienopyridines described in "both enantiomeric forms or their mixture," and by specifying that the patent covers the thienopyridines and "their addition salts with pharmaceutically acceptable mineral or organic acids." ('596 patent col. 13, lines 8-19.)

The description section of the '596 patent makes this description even more explicit, Apotex asserts, because it states that the patent describes not only the general racemic compounds specified in the patent, but also their "addition salts with pharmaceutically acceptable mineral or organic acids." It also states that "the invention relates both to each enantiomer and their mixture." ('596 patent at col. 1, lines 40-44.) Moreover, Apotex points out, the '596 patent expressly lists PCR 4099 as Example 1 in the patent. Because a person of ordinary skill in the art would know that one enantiomer of a racemic mixture would likely be more pharmaceutically active than the other, Apotex alleges, the '596 patent's indication of PCR 4099 and its two enantiomers is sufficient to lead a person of ordinary skill in the art to "the active enantiomer" of PCR 4099. Finally, Apotex alleges, the patent defines a class of only three preferred salts—bisulfate, hydrochloride and hydrobromide—because only these three salts are used in the examples for the class of ester compounds of which PCR 4099 is a member. Therefore,

Apotex claims, a person of ordinary skill in the art would gain an understanding of clopidogrel bisulfate merely by reading the ‘596 patent.

Not only would the ‘596 patent give a person of ordinary skill in the art an understanding of clopidogrel bisulfate, Apotex claims, but by reading the patent that person would be able to “practice the invention without undue experimentation,”

Advanced Display Sys., 212 F.3d at 1282, or, here, apply the teachings of the ‘596 patent and his or her background knowledge to produce clopidogrel bisulfate as disclosed in claim three of the ‘265 patent. Apotex alleges that the ‘265 patent indicates “the classic method” for separating a racemate into its enantiomers—a method that originated with Louis Pasteur in the 19th century and “is taught in every common text-book of Organic Chemistry”—and a person skilled in the art would know this method and be able to separate the enantiomers of PCR 4099 with only routine experimentation. Finally, salt formation is “an everyday matter” for one of ordinary skill in the art, Apotex claims. In sum, Apotex asserts that ordinary skill in organic chemistry together with the teachings of the ‘596 patent would enable a chemist to produce clopidogrel bisulfate. Hence, Apotex concludes, the ‘265 patent is invalid because it is anticipated by Sanofi’s own ‘596 patent.

#### *iv. Discussion*

Although Apotex has succeeded in raising a “substantial question” as to whether the ‘265 patent was anticipated by the ‘596 patent, Sanofi has adequately demonstrated that that question “lacks substantial merit.” Genentech, Inc., 108 F.3d at 1364.

As a preliminary matter, the burden of showing invalidity is “especially difficult” when “the infringer attempts to rely on prior art that was before the patent examiner

during prosecution,” as was the case here. See Glaxo Group, 376 F.3d at 1348 (citing Al-Site Corp v. VSI Int’l Inc., 174 F.3d 1308, 1323 (Fed. Cir. 1999)); see also American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1359 (Fed. Cir. 1984) (when a challenger attacks a patent on the basis of prior art that was considered by the PTO examiner, the challenger “has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job,” especially since the patent examiners “are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art”).

As noted above, Apotex asserts that the ‘265 patent is invalid because it is anticipated by the ‘596 patent; that is, the earlier patent describes the later one and also enables a person of ordinary skill in the art to produce it. We now turn to each of those concepts.

*Does the ‘596 Patent Describe Clopidogrel Bisulfate?*

As for the first prong of the test for whether the ‘596 patent anticipated the ‘265 patent, the Court finds for the purposes of this Opinion that the ‘596 patent did not describe clopidogrel bisulfate. First, the sheer number of compounds in the class covered by the ‘596 patent indicates that the patent did not point a scientist towards the bisulfate salt of the dextrorotatory enantiomer of PCR 4099. Apotex’s expert Dr. Robert McClelland agreed on cross-examination that to find the number of compounds covered by the general formula in the ‘596 patent, one would multiply the variables for X by the variables for Y and then multiply that by 50 different pharmaceutically acceptable salts.<sup>2</sup> (See tr. at 492.) Sanofi’s experts testified that this calculation yields millions of

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<sup>2</sup> Dr. McClelland agreed that this would be “one way of doing it,” and explained “I would multiply and obtain the number of compounds and then multiply to obtain the total number including salts.” (Tr. at 492.)

compounds (Davies, at ¶ 63-64 (“9.5 million”); Maffrand, tr. at 137 (“millions”)); Dr. McClelland admitted that the number of compounds totals “at least hundreds of thousands.” (Tr. at 494.)

In Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1572 (Fed. Cir. 1992), the Federal Circuit found that a prior patent that “state[d] in a very general way that fiberglass can be used as a substrate,” did not disclose the “range of mesh sizes and thickness parameters that encompassed the range of measurements claimed” in a later patent, even though the specific claims of the later patent were “subsumed in” the prior patent’s “generalized disclosure.” Id. at 1572. The Federal Circuit found that the claims in the earlier patent were “so broad as to be meaningless to one skilled in the art,” without more specific guidance. Id. Similarly, here, because the pool of options is so large, the ‘596 patent does not “sufficiently describe” a specific salt form of a specific enantiomer of a particular racemate out of all those “millions,” or at least “hundreds of thousands” of options “to have placed the public in possession of it.” Id.

Apotex claims that the ‘596 patent gave specific guidance leading a chemist to clopidogrel bisulfate by listing PCR 4099 as the first of only 21 examples, and by pairing the examples in the ester group, of which PCR 4099 is a member, with only three pharmaceutically acceptable salts, including bisulfate. However, nothing in the patent directed a chemist to separate the enantiomers of PCR 4099 or to prepare one of the enantiomers of PCR 4099 as a bisulfate salt, rather than as a hydrochloride salt as the racemate PCR 4099 was described in Example 1.

First, none of the examples in the ‘596 patent shows individual enantiomers separated from their opposite enantiomers, as Aptorex’s expert agreed. (Testimony of Dr. Robert McClelland, tr. at 495.) Aptorex’s expert Dr. McClelland agreed that the term “each enantiomer and their mixtures,” from the ‘596 patent at column 1, lines 40-41, appears only in the general description portion of the ‘596 patent, and is not referenced again in the context of any specific example. (Tr. at 496-497.) At first, Dr. McClelland testified that “the patent teaches that the compounds can exist as enantiomers,” claiming that a scientist would be led to the dextrorotatory enantiomer of PCR 4099 by reading the “each enantiomer and their mixtures statement” into the first example. That is, the scientist would understand that PCR 4099 could also exist as one or the other of its enantiomers. (Tr. at 499.) However, Dr. McClelland then admitted that this reasoning would lead a scientist as equally to the levorotatory enantiomer as to the dextrorotatory, and that, moreover, the scientist could read the “each enantiomer and their mixtures” statement equally into any of the “hundreds of thousands” of compounds disclosed in the ‘596 patent. (Tr. at 499-500; McClelland, tr. at 494.)

Indeed, Sanofi’s experts testified that nothing in the prior literature could have predicted that a single enantiomer of the racemate PCR 4099 would have more acceptable pharmaceutical properties than the racemate itself. Thus, a scientist would not have been motivated to split the enantiomers of 4099 without guidance that the ‘596 patent did not provide. Sanofi’s experts allege that the split of activity and toxicity—with a single enantiomer having nearly all of the activity and none of the toxicity—could not have been expected. (See Davies at ¶¶ 206-211; Expert Report of Shayne Gad dated July 8, 2004, attached as Ex. 1 to Decl. of Shayne Gad dated Aug. 9, 2006, at ¶¶ 118-119;

Expert Report of Stephen R. Hanson dated July 8, 2004, attached as Ex. 1 to Decl. of Stephen R. Hanson dated Aug. 8, 2006, at ¶ 58.) Apotex's own expert, Dr. McClelland, testified that although there are examples where the inactive enantiomer contributes toxicity and the active enantiomer does not, these examples are not predictable, and this split is "less predictable" than the simple split between activity and inactivity. (See tr. at 505-06.) While Dr. Maffrand testified on cross-examination that the literature in the late 1970s suggested that different enantiomers *could* have different biological properties from their racemate or from each other, he also testified that nothing in the literature could have predicted when they *would* have different properties. (Tr. at 170-72.) Dr. Maffrand testified that in "numerous" cases, including the drug Prozac, there is "no obvious difference" between the two enantiomers. (Tr. at 171.) He also testified that Sanofi performed experiments on hundreds of compounds while testing for an acceptable anti-platelet aggregation drug, and only attempted to split the enantiomers in three instances, (see tr. at 145), a fact which suggests that selecting only one enantiomer of a racemic compound was not a matter of routine. (See also Davies at ¶ 204 ("Sanofi's own thienopyridine program . . . showed that until they invented clopidogrel, their research effort was focused almost solely on modifying the thienopyridines to come up with a better compound. Only twice did they obtain the isolated enantiomers of a thienopyridine prior to making clopidogrel."))

Moreover, the Sanofi experts testified that the properties of enantiomers are unpredictable in the body, rendering a separation of enantiomers ineffective in many cases because even if the enantiomers are separated, they could convert back into the racemic mixture, via a process known as racemization. Dr. Maffrand testified that

because PCR 4099 has a C-O-Y group attached to the chiral center, PCR 4099 is susceptible to racemization, which, he explained, “means if you succeed in separating the two enantiomers they could convert back to the racemate by racemization.” (Tr. at 147-148; see also Davies at ¶ 84 (stating that “a chemist would immediately realize that . . . the PCR 4099 molecule would be susceptible to racemization . . . putting the chemist back to square one”).) Dr. Maffrand testified on cross-examination that because there are “a number of process[es] which play a role” in the metabolization of a drug once it is in a human body, the enantiomers often “revert back,” or racemize in the body. (Tr. at 171-172.) Ibuprofen, Thalidomide and Pesugryl are all examples of drugs that racemize in the body. Indeed, Dr. Maffrand stated, this is “because [scientists] are not able with two separated enantiomer[s] to avoid the racemization in the body.” (Id.) Apotex’s expert Dr. McClelland agreed, on cross-examination, that “there are examples where if you give one enantiomer, the body converts it back to racemic.” (Tr. at 505.) In sum, in Dr. Maffrand’s words, “it’s very difficult to predict if two enantiomers could have or not have the same activity in the body.” (Tr. at 171-72.)

Finally, the evidence reflects that Apotex spent many years and “tens of millions” of dollars developing PCR 4099 before discontinuing work on the racemate to focus on the single dextrorotatory enantiomer, or clopidogrel. If even those who secured the ‘596 patent did not attempt to separate the enantiomers of PCR 4099 until very late in the testing and development of the racemate, it seems evident the ‘596 patent did not give specific guidance leading a chemist to do so. Sanofi researchers decided to try separating the enantiomers of PCR 4099 after performing “at least 50 different tests,” and spending “tens of millions” on PCR 4099 research over the course of five years. (Maffrand, tr. at



143-144.) Dr. Maffrand testified that when Sanofi decided to discontinue development of PCR 4099, Sanofi had already completed “phase one clinical studies”—which meant that the company had proceeded to testing PCR 4099 in humans—and that the decision to focus on clopidogrel instead of the PCR 4099 racemate set Sanofi back four years in bringing a new antiplatelet aggregation drug to the market, something it knew was needed by the marketplace. (Tr. at 154-155; see also April 1987 Letter from Pierre Simone, Pl. Ex. 87.)

The evidence suggests that not only would a scientist not have been led by the ‘596 patent to the dextrorotatory enantiomer of PCR 4099, but the scientist would also not have been led to prepare that enantiomer as a bisulfate salt. Example 1 of the ‘596 patent described PCR 4099 as a hydrochloride salt, not a bisulfate salt. (See McClelland, tr. at 497; ‘596 patent, Example 1.) According to Sanofi’s expert Dr. Byrn, this example would suggest to a chemist that the hydrochloride would also be an acceptable salt form for clopidogrel, and thus would actually dissuade one of ordinary skill to try the bisulfate. (Byrn at ¶ 83.) Further, at the time the ‘265 patent issued, bisulfate had not been previously approved by the FDA for marketing in the United States as a pharmaceutical. (See Maffrand, tr. at 233.) A chemist could choose from between 50 different approved pharmaceutical salts in deciding how to formulate a solid dosage form of the drug. (See McClelland, tr. at 500; Byrn at ¶ 82.)

Even if a chemist were to try only the three salts used for the ester group compound examples in the ‘596 patent, the chemist could not be certain of finding a pharmaceutically acceptable salt form for clopidogrel among those three. Sanofi’s expert Dr. Byrn explains that “every salt formation with a new compound is . . . an

unpredictable exercise because of the way that salt molecules pack in the solid state. One cannot say that just because the bisulfate salt was used with the racemic compounds of the ‘596 patent, that it would be expected to work with the single enantiomer clopidogrel.” (Byrn at ¶ 85; see also Affidavit of Alain Badorc dated June 11, 2003 (“Badorc”), attached as Ex. 1 to Decl. of Alain Badorc dated Aug. 11, 2006, at ¶ 26.) Rather, a chemist would have to test various salts to find one with all of the desired properties, that is, a salt that is highly crystalline, stable, does not absorb water, and that has good solubility for use in clinical testing. (Byrn at ¶ 76.) To this end, even given the teaching of the ‘596 patent, Sanofi chemist Dr. Alain Badorc tried to formulate clopidogrel as twenty different salts before finding that the enantiomer would crystallize well and possess acceptable pharmaceutical properties as a bisulfate salt. (See Badorc at ¶¶ 27-30) Thus, disclosing bisulfate in the ‘596 patent was insufficient to disclose a single enantiomer of a disclosed compound as a bisulfate salt. See also Pfizer Inc. v. Ranbaxy Labs Ltd., 405 F. Supp. 2d 495, 517 (D. Del. 2005) (“[T]he selection of salts is a difficult task. Given the unique properties each salt imparts to the parent compound, salt selection is not a routine process and the success of a given salt is not easily predicted.”)

*Does the ‘596 Patent Enable a Person of Ordinary Skill in the Art to Produce Clopidogrel Bisulfate?*

As for the second prong of the anticipation test—whether the ‘596 patent enables a person of ordinary skill in the art to produce clopidogrel bisulfate—the Court finds for the purposes of this Opinion that the ‘596 patent did not enable clopidogrel bisulfate such that “a person of ordinary skill in the art could practice the invention without undue

experimentation.” Advanced Display Sys., 212 F. 3d at 1282. The parties agree that a person of ordinary skill in the art has a bachelor’s degree in chemistry with a specialization in organic chemistry and would have several years experience in the field “involved in the synthesis, study and properties of drugs, drug candidates, and biologically active compounds.” (McClelland, tr. at 447-48; see also Snyder at 10; Davies at ¶ 18.) This person “would have both knowledge and experience in the preparation and separation of stereoisomers.” (McClelland, tr. at 484-85; see also Davies at ¶ 18.)

First, the ‘596 patent did not disclose to a skilled person how the enantiomers of PCR 4099 could be separated. Because the properties of dextrorotatory and levorotatory enantiomers in a racemic compound will, “in general,” have identical physical properties, a chemist must devise some method for changing the enantiomers so they have “at least some different physical property, which hopefully can be exploited to separate the compounds.” (Davies at ¶ 43.) Sanofi’s experts assert that a chemist cannot be certain before experimentation which method of separation will be effective for a given compound. (Id.) As Apotex points out, Dr. Badorc employed a “classic” method to elicit the dextrorotatory enantiomer—by forming diastereomeric salts with an optically active acid followed by crystallization. However, the evidence shows that there are many such “classic” methods for separating enantiomers.<sup>3</sup> (Maffrand, tr. at 174-76; Davies at ¶ 44 (listing 13 “methods for obtaining individual enantiomers that one of ordinary skill would have considered when faced with the challenge of obtaining enantiomers”).) Dr. Maffrand testified that there was no “way to know whether any of those methods would

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<sup>3</sup> On this point, while Apotex makes much of the fact that the method Badorc employed to successfully separate the enantiomers was *the* classic method,” the only document Apotex proffered identified it as *a* classic method. (Maffrand, tr. at 175-76, 248; DX 425.)

be successful in separating any particular racemate before you tried to use it.” (Tr. at 249.) He also testified that “you can even test all the methods, all the approaches, and finally fail. You have no guarantee of success.”<sup>4</sup> (Tr. at 249-50.)

In fact, Dr. Badorc tried various methods before succeeding in separating the enantiomers (Maffrand, tr. at 128, 132; Badorc at ¶¶ 4-24.); if the ‘596 patent disclosed clopidogrel in such a way that a person of skill in the art could obtain clopidogrel from PCR 4099, or “practice the invention without undue experimentation,” Advanced Display Sys., 212 F. 3d at 1282, Dr. Badorc should have been led to a successful method of separating the enantiomers of PCR 4099 without the five to six months of experimentation he undertook. (See Badorc at ¶¶ 4-24; Maffrand, tr. at 148.) Apotex’s expert Dr. McClelland opined that Dr. Badorc’s early experiments were “inventive” and that he believed that “a skilled person with the vast knowledge of diastereomer salt separations” Dr. Badorc had “would have chosen at the beginning” the successful method Dr. Badorc ultimately chose. However, not only could Dr. McClelland not explain why, if that were true, Dr. Badorc in fact undertook extensive experiments before choosing the method that was ultimately successful, but the Court does not credit Dr. McClelland on this point, since he testified that he had performed only one enantiomeric separation in his entire professional career. (McClelland, tr. at 484-485.)

Finally, there is evidence, which is credited, that a person of ordinary skill in the art must often experiment in attempting to formulate a salt by altering a number of variables to accomplish salt crystallization, even once a particular salt form is selected. (Byrn at ¶¶ 28-29; McClelland, tr. at 509-510.)

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<sup>4</sup> Such is the scientific interest in the subject that Sanofi expert Dr. Stephen Davies estimates that there are “tens of thousands of publications in the scientific literature . . . concerning the application of these methods to obtain enantiomers of specific compounds.” (Davies at ¶ 45.)

*v. Conclusion*

The Federal Circuit has cautioned that courts should not indulge “the mechanistic dissection and recombination of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant’s disclosures.” In re Ruschig, 343 F.2d 965, 974 (C.C.P.A. 1965); see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 364 F. Supp. 2d 820, 900 (D. Ind. 2005). Apotex’s case for anticipation appears to rest on just such hindsight. Dr. McClelland admitted as much in the following testimony:

Q. If somebody skilled in the art was doing the kind of analysis you did but didn’t know that the answer was clopidogrel but just took all the examples of the ‘596 patent and dismembered them and put them back together the way you did, you wind up with over 300 compounds, isn’t that right?

A. I’m getting 160.

Q I think you’re shortchanging me Doctor, but I’ll take 160. Now, would you agree with me, Doctor, that if somebody had asked you, in 1988, showed you the compound clopidogrel and a list of 50 salts . . . and asked you which one of those is going to be useful as a drug substance, you could not have predicted that?

A. That’s correct.

(Tr. at 503.)

Because of the number of compounds disclosed by the ‘596 patent, the lack of specific guidance by the ‘596 patent as to either the beneficial properties of clopidogrel or the method of separating the enantiomers of PCR 4099, and the failure of the ‘596 patent to indicate the bisulfate salt as a pharmaceutically acceptable form for clopidogrel, the Court finds that Sanofi has adequately established for the purposes of a preliminary injunction that Apotex’s contention that the ‘265 patent is invalid because it was

anticipated by the '596 patent "lacks substantial merit." See Genentech, Inc., 108 F.3d at 1364.

b. Obviousness

Section 103 of 35 U.S.C. provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103. "Obviousness is a question of law which is predicated upon several factual inquiries." Pfizer Inc. v. Ranbaxy Labs., 405 F. Supp. 2d at 516 (citing Richardson-Vicks v. UpJohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997)).

Specifically, in determining whether a patent is invalid as obvious over the prior art, a trier of fact must consider (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) secondary considerations of non-obviousness, such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid. See Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). The Court must also consider whether one skilled in the art would have been motivated to modify the '596 patent to obtain clopidogrel bisulfate. See Abbott Labs. v. Andrx Pharms., Inc., 452 F.3d 1331, 1336 (Fed. Cir. 2006)

To this end, "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. Rather, a party alleging invalidity due to obviousness must articulate the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them." Id. at 1336 (citing In re Kahn, 441 F.3d 977, 986 (Fed. Cir. 2006)); see also Pfizer Inc. v.

Ranbaxy Labs, 405 F. Supp. 2d at 517. However, “[o]bvious to try’ has long been held not to constitute obviousness,” and a “general incentive does not make obvious a particular result.” In re Dueul, 51 F.3d 1552, 1559 (Fed. Cir. 1995). Rather, to establish obviousness, “a claimed specific compound” must be “precisely envisioned” by the prior art. Id. at 1559.

According to Apotex, clopidogrel bisulfate was rendered obvious by the ‘596 patent because, after gaining familiarity with that patent, a person of ordinary skill in the art would view as obvious the active enantiomer of PCR 4099 in the form of each of the three salts used for ester compounds in the examples of the ‘596 patent—namely, hydrochloride, bisulfate and hydrobromide. A person of ordinary skill would know that PCR 4099 held the most promise among the compounds disclosed by the ‘596 patent, would know that separating the enantiomers of PCR 4099 would elicit one active and one inactive enantiomer, and would view as obvious the preparation of that active enantiomer of PCR 4099 as each of the disclosed salt forms. Moreover, the ‘596 patent expressed the purpose behind the exercise—the search for a platelet aggregation inhibitor with a better activity/toxicity ratio than other drugs currently on the market. Thus, according to Apotex, the ‘596 patent also provided the motivation for a person of ordinary skill to synthesize clopidogrel bisulfate.

Sanofi does not contradict Apotex’s assertion that after becoming familiar with the ‘596 patent a person of ordinary skill would be motivated to find a better antiplatelet aggregation compound, and would understand that PCR 4099 was the compound with the most promise among the extensive number of compounds in the genus thienopyridines. However, Sanofi alleges that there was nothing obvious about arriving at clopidogrel

bisulfate by separating the enantiomers of PCR 4099 and preparing the dextrorotatory as a bisulfate salt.

The Court agrees, finding that at this stage Apotex has not succeeded in raising a substantial question as to the validity of the ‘265 patent on the basis of obviousness.

First, the Court finds that it would not have been obvious to a person skilled in the art that a more pharmaceutically acceptable compound could be obtained by separating the enantiomers of PCR 4099. As previously set forth, the prior art could not predict whether a single enantiomer of the racemate PCR 4099 would have more acceptable pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity. (See supra at III.B.2.a.iv.) Moreover, the prior art could not have made obvious whether or not a separated enantiomer of PCR 4099 would racemize in the body, serving to neutralize whatever gains might have been achieved by separating the enantiomers in vitro. (See id.) Evidence of Sanofi’s research course prior to securing the ‘265 patent illustrates the fact that separating the enantiomers of PCR 4099 was not obvious at the time. Apotex spent four years and millions of dollars developing and extensively testing the racemate PCR 4099 before deciding to try separating the enantiomers of that racemic compound. (See id.) Although theoretically possible, it nonetheless severely strains credulity to imagine that Sanofi would have invested such extensive resources into developing the racemate if it were obvious at the time to a person of ordinary skill in the art that the proper course to obtain a superior antiplatelet aggregation drug would be to elicit the dextrorotatory enantiomer instead.



Second, the Court finds that it would not have been obvious to a person skilled in the art that the dextrorotatory enantiomer could be developed into an acceptable tablet form by synthesizing it as a bisulfate salt, instead of other available salts. The evidence shows that salt formation is an unpredictable exercise, and that a chemist would not know, before testing various acids and bases, which one would cause a specific compound to crystallize and have pharmaceutically acceptable properties. (See id.) Again, evidence of Sanofi's own research course demonstrates that the prior art did not render salt selection obvious, as Dr. Badorc tested 20 different salts before finding that the bisulfate had the desired pharmaceutical properties. (See id.) On cross-examination Dr. McClelland admitted that although he believed the '596 patent would lead a person skilled in the art "to try the hydrochloride, hydrobromide . . . the oxalate and the bisulfate salts in a preliminary screen," making salts "is unpredictable" and a chemist would have to engage in experimentation to determine which salt would in fact be suitable. (Tr. at 508-510.)

In sum, the Court finds that it would not have been obvious prior to extensive experimentation that clopidogrel bisulfate would have the pharmaceutically superior properties it did in fact have. The '596 patent did not enable a person of ordinary skill in the art to "precisely envision[]" clopidogrel bisulfate. In re Dueul, 51 F.3d at 1559.

As for the "secondary considerations of non-obviousness," Graham, 383 U.S. at 17-18, the Court finds that such considerations do not weigh either for or against the obviousness of clopidogrel bisulfate based on the prior art. Because Sanofi held the '596 patent, which covered the genus of compounds of which clopidogrel was a member, no other entity could have brought a similar drug to market throughout the duration of that

patent. Thus, the “failure of others,” “long felt but unresolved need,” and “commercial success” of clopidogrel, see Graham, 383 U.S. at 17-18, could have been derived from Sanofi’s ‘596 patent as much as from the non-obviousness of clopidogrel bisulfate. See Merck & Co. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1377 (Fed. Cir. 2005) (though commercial success may generally support a conclusion that a claimed invention was non-obvious, the inference fails when others are legally barred from testing or practicing the invention given the existence of another patent covering that invention).

The irrelevance of the secondary considerations does not alter the Court’s finding that Sanofi has succeeded in proving, for the purposes of a preliminary injunction, that the questions Apotex has raised as to the validity of the ‘265 patent on the ground of obviousness “lack[] substantial merit.” Genentech, Inc., 108 F.3d at 1364.

### c. Double-Patenting

The judicial doctrine of obviousness-type double-patenting prevents a patent claim from validly issuing when it “is obvious over, or anticipated by” a claim in an earlier patent. Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 968 (Fed. Cir. 2001). The test for obviousness-type double-patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. See Geneva Pharm., Inc. v. Glaxosmithkline PLC, 349 F.3d 1373, 1378 (Fed. Cir. 2003) (“Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application.”); Affymetrix, Inc. v. PE Corp., 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at \*5 n.3 (S.D.N.Y. Dec 24, 2002) (“The same type of analysis is used for an obviousness-type double patenting inquiry as for a § 103 obviousness inquiry,

except that the scope of a double patenting inquiry is limited to only the claims of the first patent, rather than the entirety of its disclosure.”).

The judicially created double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi’s entire ‘596 patent was prior art at the time the ‘265 patent issued. If Apotex fails to prove at trial that the ‘265 patent was obvious in light of the ‘596 patent as a whole, it has also necessarily failed to prove that the ‘265 patent was obvious in light of the specific claims of the ‘596 patent. Because the questions Apotex has raised as to the validity of the ‘265 patent on the ground of section 103 obviousness lack substantial merit, the Court will not engage in a redundant double-patenting inquiry.

### **3. Unenforceability**

#### **a. General Principles**

A patent applicant must prosecute patent applications with candor, good faith, and honesty. See 37 C.F.R. § 1.56; see also Elk Corp., 168 F.3d at 30 (citing Molins PLC v. Textron, Inc., 48 F.3d 1172 (Fed. Cir. 1995)). A breach of this duty may constitute inequitable conduct rendering the patent unenforceable. Specifically, “[a] patent may be rendered unenforceable for inequitable conduct if an applicant, with intent to mislead or deceive the examiner, fails to disclose material information or submits materially false information to the PTO during prosecution.” Jumpsport, Inc. v. Jumpking, Inc., 2006 U.S. App. LEXIS 18448, at \*18 (Fed. Cir. July 21, 2006) (citing Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1313 (Fed. Cir. 2006)).

To demonstrate a failure to disclose material information, the party asserting inequitable conduct must show “(1) prior art that was material; (2) knowledge chargeable

to an applicant of that prior art and of its materiality; and (3) failure of the applicant to disclose the art resulting from an intent to mislead the PTO.” Elk Corp., 168 F.3d at 30 (citations omitted). Apotex must show “a threshold level of materiality and intent by clear and convincing evidence.” Jumpsport, 2006 U.S. App. LEXIS 18448, at \*19.

Sanofi may rebut proof of inequitable conduct by “a showing that (a) the prior art was not material, (b) if the prior art was material, a showing that the applicant did not know of that art; (c) if the applicant did know of the art, a showing that the applicant did not know of its materiality; or (d) a showing that the applicant’s failure to disclose the art did not result from an intent to mislead the PTO.” Elk Corp., 168 F.3d at 30.

“Information is ‘material’ when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent.” Elk Corp., 168 F.3d at 31 (citing Molins, 48 F.3d at 1179). “[A]n otherwise material reference need not be disclosed if it is merely cumulative of or less material than other references already disclosed.” Elk Corp., 168 F.3d at 31 (citing Halliburton Co. v. Schlumberger Tech. Corp., 925 F.2d 1435, 1440 (Fed. Cir. 1991); Baxter Int’l, Inc. v. McGaw, Inc., 149 F.3d 1321, 1328 (Fed. Cir. 1998)). With regard to intent to deceive the PTO, the Court must infer intent “from the facts and circumstances surrounding [Sanofi’s] overall conduct.” Elk Corp., 168 F.3d at 32 (citing Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 984 F.2d 1182, 1190 (Fed. Cir. 1993)). However, the Court will not infer intent to deceive without clear and convincing evidence. See Baxter Int’l Inc., 149 F.3d at 1329 (“[T]here must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference.”); Old Town Canoe Co. v. Confluence Holdings Corp., 448 F.3d 1309, 1322

(Fed. Cir. 2006) (affirming district court’s finding of no intent to deceive when party did “little more than urge this court to draw an inference of intent to deceive, arguing that the applicant or his attorney knew, or should have known that withheld information would be material”).

Because the question of whether inequitable conduct occurred is an equitable one, it is committed to the discretion of the district court. See Elk Corp., 168 F.3d at 30-31 (citing Kingsdown Med. Consultants, Ltd. v. Hollister, Inc., 863 F.2d 867, 876 (Fed. Cir. 1988) (en banc)).

#### b. Analysis

To defeat Sanofi’s motion for a preliminary injunction, Apotex must show a “substantial question” as to inequitable conduct. Genentech, Inc., 108 F.3d at 1364. Apotex alleges that Sanofi made several materially false statements and omitted material facts in an intentional effort to deceive the PTO examiner. It first claims that Sanofi falsely represented to the PTO that the therapeutic activity of the dextrorotatory enantiomer was “unexpected.” Second, Apotex asserts, Sanofi falsely informed the PTO examiner that the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers were surprising. Finally, Sanofi allegedly concealed that Dr. Maffrand was a true inventor of clopidogrel. Because Sanofi failed to name Dr. Maffrand as an inventor in the ‘265 patent, it was able to conceal both his knowledge that there was nothing unexpected about the properties of clopidogrel as well as a journal article on this topic that Maffrand knew about and that should have been submitted as relevant prior art. Taking each of these allegations in turn, the Court concludes that Apotex has not raised a “substantial question” as to inequitable conduct by Sanofi in prosecuting the ‘265 patent.

*i. “Unexpected” Therapeutic Activity*

Apotex gives two reasons for its assertion that Sanofi knew that characterizing the therapeutic activity of clopidogrel as “unexpected” was false. First, they point to a 1987 memorandum from Sanofi’s French patent attorney Jacqueline LaForest to another Sanofi attorney that was exchanged as the two prepared an application for the French priority patent on clopidogrel bisulfate. Ms. LaForest replied to a draft of the French patent application with the handwritten remark, “[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner’s hurdles without other results.” (See Maffrand, tr. 93-94; DTX 304, translation at DTX 305.) Apotex alleges that this remark can only be taken as a reply to the draft phrase, “[i]n an unexpected manner only the dextro-rotatory enantiomer exhibits platelet aggregation inhibiting activity, the levo-rotatory enantiomer being inactive.” However, this remark was made in January 1987, before the results of March 1987 toxicology studies were known. (See Maffrand, tr. at 152.) These toxicology studies revealed what was “unexpected” about clopidogrel, and that was the remarkable split between activity and toxicity between the two enantiomers of the racemate. (Davies at ¶¶ 209, 227-229.) Sanofi alleges that the ‘265 patent issued upon Sanofi’s representation that this split was unexpected. Moreover, there is no evidence that Ms. LaForest, who was an attorney, had sufficient scientific expertise to judge the evidence upon which she based her comment. The Court finds that in light of this evidence, the statement by Ms. LaForest is not probative of Sanofi’s intent to deceive the U.S. patent examiners and is certainly not “clear and convincing” evidence of an intent to deceive. See Baxter Int’l Inc., 149 F.3d at 1329

Apotex also claims that Sanofi's characterization of the therapeutic properties of clopidogrel as "unexpected" was false in light of Sanofi's prior work on thienopyridine compounds. Specifically, Apotex claims that Sanofi knew that pharmaceutical activity is commonly concentrated in a single enantiomer because of its earlier work separating the enantiomers of PCR 1033, which was also a racemic compound. However, Sanofi defends its characterization on the ground that there is simply no way to predict where the activity and the toxicity of a racemate will reside when the enantiomers are separated, and that it is more usual for a single enantiomer to have both the activity and toxicity. (See Maffrand, tr. at 170-72; Davies at ¶¶ 206-11; Hanson at ¶ 58.) Moreover, Sanofi's experience with PCR 1033 had very little bearing on its expectations as to the characteristics of enantiomers of PCR 4099, because, as Sanofi's expert Dr. Davies explained, "the functional difference between PCR 1033 and PCR 4099 is so significant that no reasonable medical chemist could expect that they would behave in the same manner in the body." (Davies at ¶¶ 225-28.) The Court finds that Sanofi's experience with PCR 1033 did not render materially false its characterization of the therapeutic properties of clopidogrel as "unexpected."

*ii. Tolerance*

Apotex's second allegation of inequitable conduct before the PTO concerns Sanofi's statement that the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers was surprising. Apotex argues that Sanofi had not yet conducted any tolerance testing at the time of the patent application, and thus had no data to support any assertions regarding how well clopidogrel was tolerated.

However, at the time of its '265 patent application, Sanofi had evidence from pharmacological and toxicity studies that was relevant to how well clopidogrel was tolerated. Dr. Maffrand testified that “formal toxicity studies and data are included in the general broad sense attributed to tolerance.” (Tr. at 254-55.) Moreover, Dr. Maffrand testified that “Tolerance . . . refers to side effects which can be observed during the pharmacological studies, for example during platelet aggregation assay[s]. . . and, of course, they could be observed during toxicological studies.” (*Id.*) Given the relationship between the two concepts of toxicity and tolerance, the Court is unable to conclude that Sanofi reported the superior tolerance of clopidogrel with an intent to deceive the PTO examiner.

*iii. Dr. Maffrand's Knowledge*

Apotex's third inequitable conduct allegation is that Sanofi concealed that Dr. Maffrand was a true inventor of clopidogrel bisulfate, and that concealing his status facilitated Sanofi's concealment of his knowledge that there was nothing unexpected about the properties of clopidogrel, based on his prior work with PCR 1033. In addition, Apotex alleges, withholding Dr. Maffrand's name enabled Sanofi to conceal a relevant prior art journal article by Robert W. Colman and William R. Figures entitled “Characteristics of an ADP Receptor Mediating Platelet Activation” that Maffrand knew about. This article was “highly material,” Apotex claims, because it provided a basis for understanding the likely activity of various molecules—by describing characteristics of protein receptors relevant to platelet aggregation—which a reasonable PTO examiner would have found important.



The Court finds that Dr. Maffrand credibly testified that he did not include himself on the patent application because he did not consider himself to be the inventor of clopidogrel bisulfate. Dr. Maffrand testified that although it was he who directed Dr. Badorc to try to separate the enantiomers of PCR 4099, he did not participate on a technical level in the invention and he did not give any advice on how to attempt to separate the enantiomers of the racemate. (Tr. at 152.) It was Dr. Badorc and Dr. Fréhel who in fact conducted the various experiments and ultimately succeeded in separating the enantiomers, and it was Dr. Badorc and Dr. Fréhel themselves who put their names on the patent application and prepared the draft application. (*Id.*) The Court finds that there is no evidence that Dr. Maffrand was not named as an inventor because Sanofi had an intent to deceive the patent office.

This is especially the case because one of Sanofi's experts testified that Sanofi's experience with separating the enantiomers of PCR 1033 did not render Sanofi's results with PCR 4099 expected. (*See supra* at III.B.3.b.i.) Thus, the Court is unpersuaded by Apotex's rank conjecture that Sanofi concealed the inventorship of Dr. Maffrand in order to conceal results of prior experiments it did not believe to be relevant.

As to the prior art journal article by Coleman and Figures, neither party has adduced evidence that would enable the Court to determine whether a PTO examiner may have found this prior art reference relevant. Therefore, the Court finds that Apotex has not met its burden of raising a "substantial question" as to whether Sanofi intended to mislead the PTO office in failing to disclose this reference.

### c. Conclusion

Apotex has failed to raise a “substantial question” as to the enforceability of the ‘265 patent for the purposes of this motion. See Genentech, Inc., 108 F.3d at 1364.

### **C. Irreparable Harm**

“The patent statute provides injunctive relief to preserve the legal interests of the parties against future infringement which may have market effects never fully compensable in money.” Reebok, 32 F.3d at 1556 (citing Hybritech, 849 F.2d at 1457). “Because the principal value of a patent is its statutory right to exclude, the nature of the patent grant weighs against holding that monetary damages will always suffice to make the patentee whole.” Hybritech, 849 F.2d at 1456-57; see also H.H. Robertson, Co. v. United Steel Deck, Inc., 820 F.2d 384 (Fed. Cir. 1987), overruled on other grounds by Markman v. Westview Inst., Inc., 52 F.3d 967 (Fed. Cir. 1995) (en banc), aff’d, 517 U.S. 370 (1997). The Federal Circuit has consistently held that a party that moves for a preliminary injunction and clearly establishes likelihood of success on the merits “receives the benefit of a presumption on the second” factor, irreparable harm. Reebok, 32 F.3d at 1556; Pfizer Inc. v. Teva Pharms. USA, Inc., 429 F.3d 1364, 1381 (Fed. Cir. 2005) (“We have consistently held that a district court should presume that a patent owner will be irreparably harmed when, as here, a patent owner establishes a strong showing of likely infringement of a valid and enforceable patent.”). While the presumption is rebuttable, it shifts the ultimate burden of production onto the infringer. See id. (citing Rosemount, Inc. v. United States Int’l Trade Comm’n, 910 F.2d 819, 822 (Fed. Cir. 1990); Roper Corp. v. Litton Sys., Inc., 757 F.2d 1266, 1272 (Fed. Cir. 1985)).

Having found that Sanofi has clearly established a likelihood of success on the merits, the Court also finds that Sanofi receives the benefit of a presumption of

irreparable harm. Not only does Sanofi receive the benefit of that presumption, but it has also offered independent evidence of irreparable harm, namely, evidence that this Court credits that it will suffer irreversible price erosion, loss of good will, and will be forced to lay off personnel and discontinue research devoted to developing other medical uses for Plavix.

As to irreversible price erosion, Sanofi has submitted evidence, which the Court credits, that it has been forced to offer rebates and discounts to persuade third-party payors—such as pharmacy benefit managers and health maintenance organizations, who pay in part for 85% of all purchases of prescription drugs in the U.S.—to maintain Plavix on a favorable drug formulary pricing tier. (Decl. of Hugh O’Neill dated Aug. 13, 2006 at ¶¶ 7, 19.) This pricing tier affects the amount an insured consumer must pay when he or she purchases a prescription drug. (O’Neill at ¶¶ 8-11.) The introduction of a generic product will ordinarily lead third-party payors to place Plavix in a less favorable tier, causing patients to pay a higher copay for the drug. (*Id.*) Sanofi has shown, on the evidence adduced so far, that this change will have several irreversible effects on Sanofi. First, if Sanofi decides to provide discounts or rebates to persuade third-party payors to maintain Plavix on a favorable pricing tier, it will face pressure from those third-party payors to continue the discount or rebate scheme, even if Apotex were ordered to discontinue distributing generic clopidogrel. (O’Neill at ¶¶ 16-21.) If Sanofi decides to keep Plavix at its current price, there is the possibility that it will suffer losses due to unfavorable tier placement, and will have difficulty persuading third-party payors to restore the original tier placement in the event the generic clopidogrel product can no longer be distributed, due to the presence in the marketplace of existing supplies of the

generic. (Id.) (Id. at ¶ 21; Testimony of Dr. Jerry A. Hausman, tr. at 304; Decl. of Jerry A. Hausman dated Aug. 14, 2006 at ¶¶ 22-23 (describing this as “overhang” inventory).) Moreover, demand for Plavix may decrease if Plavix is placed in a less favorable pricing tier. There are substitutes for Plavix available, and patients may request, or doctors prescribe, these substitutes. In addition, Dr. Hausman testified that many patients stop taking Plavix after a short period of time, often before their prescription for the drug has expired, in part because a patient cannot “see” the results of Plavix as, for example, one can “see” the results of a cholesterol lowering drug by taking blood tests that indicate whether cholesterol levels have in fact been lowered by the drug. (Tr. at 304-05.) For this reason, if the amount of the copay a consumer must pay rises, the consumer may stop taking the drug even earlier. (Id.)

In addition to irreversible price erosion, Sanofi has shown for the purposes of this motion that it will be irreparably harmed by loss of consumer good will by customers who will have grown accustomed to lower prices for clopidogrel bisulfate with a generic product on the market, by layoffs of employees involved in marketing Plavix, and by the potential suspension of clinical trials for new applications for Plavix—trials that Sanofi will have reduced economic incentive to conduct if there is a threat of the continuing presence of a generic on the market while Sanofi’s patent is valid and enforceable. (Decl. of Jerome Durso dated Aug. 13 2006 at ¶¶ 14-15, 17-18, 21.)

Apotex has not produced evidence sufficient to rebut the presumption of irreparable harm to Sanofi, or to adequately explain away the other forms of irreparable harm for which Sanofi has adduced credible evidence. Apotex’s attempt to rebut the presumption of irreparable harm centers on two arguments: First, Apotex claims that

Sanofi bargained away its claim for irreparable harm in the Second Agreement (i.e., the May 26, 2006 settlement agreement between the parties), by agreeing to limit its claim for damages to a fixed amount, namely 50% of Apotex's net sales of generic clopidogrel. (See Second Agreement at ¶ 14(ii).) Second, Apotex claims that Sanofi's harm is purely economic.

As to Sanofi's first argument, paragraph 14(ii) of the Second Agreement is simply a negotiated liquidated damages clause "[i]f the litigation results in a judgment that the '265 patent is not invalid or unenforceable." (Second Agreement at ¶ 14(ii).) It limits the amount of monetary damages payable by Apotex from the time of Apotex's launch of a generic up to the time an injunction is entered to "50% of Apotex's net sales of clopidogrel products." It says nothing about whether the harm to Sanofi in the absence of an injunction would be irreparable. Indeed, this interpretation is buttressed by the fact that the statutory reference in paragraph 14(ii) to 35 U.S.C. § 284 refers to the statutory provision regulating monetary, not equitable, damages. In fact, the Second Agreement specifically anticipates and regulates a motion by Sanofi for a preliminary injunction. Paragraph 15(i) provides that "Sanofi will not seek a temporary restraining order or a preliminary injunction" until 5 business days after "Regulatory Denial." Paragraph 15(ii) sets forth that "Sanofi . . . will not file for a preliminary injunction until Sanofi gives Apotex 5 business days notice . . . of its intention to do so, which notice will not be given before Apotex has initiated a launch of a generic clopidogrel product." If the parties were agreeing that there would be no irreparable harm to Sanofi in the event of a launch, a preliminary injunction would not be able to issue, and this clause would be meaningless.

In sum, Sanofi did not agree in the Second Agreement that its harm in the face of a launch of a generic by Apotex would not be irreparable.

Finally, Apotex's contention that the harm to Sanofi is merely economic fails to address Sanofi's claims of continuing irreversible price erosion, which, as the Federal Circuit recognizes, is a legitimate basis for a finding of irreparable harm, see Purdue Pharma, 237 F.3d at 1368 ("Given the testimony of the likelihood of price erosion and loss of market position . . . , we see no deficiency in the district court's finding of irreparable harm."), as the Court has credited.

Because Sanofi has demonstrated a likelihood of success on the merits, and thereby secured the statutory presumption of irreparable harm, and has, moreover, proffered further persuasive evidence of irreparable harm, the Court concludes for the purposes of this motion that Sanofi will indeed suffer such harm in the absence of a preliminary injunction.

#### **D. Balance of Hardships**

The third factor the Court must consider on a motion for a preliminary injunction is whether the balance of hardships tips in favor of one party or the other. See Hybritech, 849 F.2d at 1457. In evaluating this factor, "the district court must balance the harm that the non-moving party will incur if the injunction is granted." Id. at 1457.

It cannot be gainsaid that Apotex faces significant harm if the injunction is granted. First, Apotex's launch of its generic product triggered the beginning the 180-day period of market exclusivity afforded to it by the Hatch-Waxman Act, see 21 U.S.C. § 355(j)(5)(B)(iv); see also In re Tamoxifen, 429 F.3d at 376. The 180-day period will continue to run throughout the course of litigation, regardless of whether or not this

injunction issues. As a consequence, if the injunction does issue, Apotex will lose any profit it would have made on the tablets it could have sold in that time. (Testimony of Dr. Frank A. Bernatowicz, tr. at 405-06.) Apotex will also lose a certain amount of the market share it would have captured during its period of exclusivity under the Hatch-Waxman Act. Apotex's economic expert Dr. Frank Bernatowicz testified that he believes Apotex will capture 55% of the market for generic clopidogrel after the 180-day period of market exclusivity expires if the company sells tablets throughout that period, but will capture only 10-15% of the market if it enters at the same time as the anticipated 9 or 10 other competitors who he believes may also enter the market after the expiration of the 180-day period. (Tr. at 406-07.)

In addition to losing profits and market share from the 180-day period of market exclusivity, Apotex will lose the value of its investment in its supply of clopidogrel bisulfate for the United States market, at least insofar as that supply is subject to an expiring shelf-life. (Sherman at ¶ 56.) Finally, if an injunction is granted, Apotex will suffer loss of customer goodwill from the sudden withdrawal of its product from the market. (Id.)

All of the harms Apotex cites are harms that would not have accrued if Apotex had waited until the conclusion of this litigation to launch its product, rather than conducting—as it is entitled under the Hatch-Waxman Act—an at-risk launch in advance of a determination on the merits of its defenses in this litigation that the '265 patent is invalid and unenforceable. It was Apotex's considered choice to trigger the 180-day period of exclusivity and risk losing this period, rather than waiting until the conclusion of the action and launching after its right to do so was secure. Moreover, Apotex would

not have lost the value of its investment in a supply of clopidogrel bisulfate with an expiring shelf-life if Apotex did not amass this supply in anticipation of an at-risk launch, and Apotex would not lose customer goodwill from the withdrawal of a product it had not introduced. If Apotex had not already launched its product, it would currently be suffering harm from a delay in entering the market, and thus a reduction in its total profit for generic clopidogrel, but this harm would have been much less significant than the post-launch harms Apotex now cites.

In short, Apotex's harms were almost entirely preventable, and were incurred by the company's own calculated risk. Sanofi, on the other hand, suffers irreparable harm from the infringement of a patent that the Court has found to likely be valid and enforceable based on the state of this record. In balancing the hardships the non-moving party will incur if the injunction is granted against the hardships the moving party will incur if the injunction is not granted, the Court finds that the balance favors issuance of a preliminary injunction.

#### **E. Public Interest**

The fourth factor to be considered on a motion for a preliminary injunction is “the impact of the injunction on the public interest.” Hybritech, 849 F.2d at 1458. “Typically, in a patent infringement case, although there exists a public interest in protecting rights secured by valid patents, the focus of the district court's analysis should be whether there exists some critical public interest that would be injured by the grant of preliminary relief.” Id. (citations omitted). There are significant public interests on both sides in this litigation, but this Court finds that they balance in the context of this action in favor of Sanofi.



Apotex asserts that the public interest “unquestionabl[y]” lies in reducing the barriers to generic competition in the pharmaceutical industry, since the public will then have access to valuable drugs at reduced prices. This is most certainly a logical position for a manufacturer of generic drugs to take and, indeed, the Court finds that there is a substantial public interest in the public having access to lower priced generic drugs. Indeed, the Hatch-Waxman Act clearly expresses Congress’s judgment that generic competition is to be encouraged. In addition, in Apotex’s view, the refusal of the state attorneys general to approve the proposed settlement between Sanofi and Apotex suggests that the regulators determined that the public interest was best served by preventing the agreement’s barrier to possible competition.

The public interest in lower-priced drugs is certainly significant. As of the time of the preliminary injunction hearing, the generic clopidogrel product was \$1.10 cheaper per pill than the price of Plavix before the generic launch, and Apotex expects the price of the generic to fall more after the 180-day period of exclusivity expires. (Bernatowicz, tr. at 417-18.) Testimony at the hearing indicated that there are 48 million daily users of Plavix in the United States (*id.* at 417) and, at the time of the hearing, the testimony was that 78.4% of all clopidogrel bisulfate prescriptions were being filled by the generic product. (Hausman, tr. at 309.) In sum, in the past few weeks a large number of Americans have seen a significant savings in the cost of an important pharmaceutical.

Nevertheless, the public interest in lower-priced drugs is balanced by a significant public interest in encouraging the massive investment in research and development that is required before a new drug can be developed and brought to market. The Federal Circuit recently considered these competing interests in Pfizer Inc. v. Teva Pharms, 429 F.3d

at 1364. In that case, just as here, a company wishing to issue a generic version of a patented drug contended that the public interest favored denying a preliminary injunction on the theory that the Hatch-Waxman Act framework “makes low cost generic drugs available to the public through increased competition.” Id. at 1382. The district court rejected this argument, finding that a preliminary injunction that enforces a valid patent against an infringer “does no more than further public policy inherent in the patent laws designed to encourage useful inventions by rewarding the inventor with a limited period of market exclusivity.” Id. at 1382. The Federal Circuit affirmed, finding that “[w]hile the statutory framework . . . does seek to make low cost generic drugs available to the public, it does not do so by entirely eliminating the exclusionary rights conveyed by pharmaceutical patents. Nor does the statutory framework encourage or excuse infringement of valid pharmaceutical patents.” Pfizer Inc. v. Teva Pharms., 429 F.3d at 1382 (citing Payless ShoeSource, Inc. v. Reebok Int’l Ltd., 998 F.2d 985, 991 (Fed. Cir. 1993) (“Selling a lower priced product does not justify infringing a patent.”)).

Sanofi invested “hundreds of millions of dollars” to develop Plavix and secure FDA approval for the drug. (Durso at ¶ 8.) Although Sanofi has already more than recouped that investment after 11 years of Plavix being on the market (see Hausman, tr. at 319), Plavix is, as Sanofi’s economist Dr. Hausman described, a necessary “blockbuster drug”—a drug whose profits enable Sanofi to expend the research and development costs for drugs that in fact never make it to market, or that make it to market but never recoup the costs associated with their getting there. (Hausman, tr. at 317.) Dr. Hausman testified that the average cost to bring a drug to market is \$800 million, and that for every drug that does make it to market many others do not. (Id. at 316-17.) Finally,

protecting the patent for Plavix secures the public interest in innovation by providing commercial incentive for Sanofi to begin and continue clinical trials researching new uses for the drug. (Durso at ¶¶ 14-15.)

As set forth above, both the public interest in lower cost drugs on one hand and the public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents on the other, are present here. Because Congress has fashioned the patent laws in such a way as to balance the public's interest in market competition with the public's interest in continuing innovation, and in the context of this action, where Apotex concedes that its product infringes Sanofi's patent, the Court finds the public interest lies slightly in favor of Sanofi.

#### **IV. DEFENSES**

##### **A. Laches**

Apotex claims that the Court should not award Sanofi's preliminary equitable relief because such relief is barred by the equitable doctrine of laches. Specifically, Apotex claims Sanofi is barred from receiving a preliminary injunction because it waited too long to bring this motion. The Court disagrees.

"Laches is cognizable under 35 U.S.C. § 282 as an equitable defense to a claim for patent infringement," and, when successfully invoked, serves to bar a patentee's claim for damages prior to suit. A.C. Aukerman Co. v. R.L. Chaides Constr. Co., 960 F.2d 1020, 1028 (Fed. Cir. 1992) (en banc). The laches defense "has two underlying elements: first, the patentee's delay in bringing suit must be 'unreasonable and unexcusable,' and second, the alleged infringer must have suffered 'material prejudice attributable to the delay.'" Intirtool, Ltd. v. Texar Corp., 369 F.3d 1289, 1297 (Fed. Cir. 2004) (citing A.C.

Aukerman, 960 F.2d at 1028). The length of time which may be deemed unreasonable “depends on the circumstances,” and a “court must also consider and weigh any justification offered by the plaintiff for its delay.” A.C. Auckerman, 960 F.2d at 1032-33. Negotiations between the parties have been recognized as a legitimate excuse to a delay in bringing suit. See id. at 1033.

Apotex asserts that Sanofi caused Apotex material prejudice by refusing to move for a preliminary injunction earlier in the course of this litigation, thereby avoiding having to post a bond or “fulfill any of the other requirements for equitable relief.” Apotex asserts that Sanofi should have moved for a preliminary injunction when the 30 month stay barring FDA approval of Apotex’s ANDA expired in May of 2005; when Sanofi received Apotex’s October 2005 letter requesting that it move for a preliminary injunction or assure Apotex that it would not do so at a later time; or at another time prior to Apotex’s launch of a generic clopidogrel product on August 8, 2006. Because Sanofi did not so move, Apotex claims, it was put to the burden of “invest[ing] an enormous amount in amassing the appropriate inventory of clopidogrel,” contracting for supplies of raw material and production capacity, and scaling back work on other projects to prepare for a clopidogrel launch. Further, Apotex asserts that it will suffer prejudice by a post-launch injunction because it will effectively lose its 180-day period of exclusivity (assuming a final judgment is not rendered in this action during the next five months), which was triggered at launch, will lose the “follow-up” clopidogrel market, will suffer injury to customer relationships and will lose revenues from the sale of other products bundled with clopidogrel.

Any delay by Sanofi in bringing this motion for a preliminary injunction was not “unreasonable and unexcusable.” Intirtool, Ltd., 369 F.3d at 1297. Sanofi had no substantial reason to move to enjoin Apotex from launching a generic clopidogrel product prior to January 20, 2006, as the FDA had not yet approved Apotex’s ANDA, and thus Apotex could not launch a generic before that date. Even before the FDA approved Apotex’s ANDA, the parties initiated settlement negotiations, exchanging an interim agreement on January 20 and 23, 2006 that included the provision that during settlement negotiations “Apotex will not launch its generic product and Sanofi will not launch an authorized generic and will not move for an injunction.” (Exs. 1 & 2 to Baechtold Decl.) Then, in a second agreement on, February 8, 2006, Sanofi agreed to jointly request with Apotex that the Court postpone the trial of this action from March to June 2006 based on Apotex’s counsel’s scheduling conflict, and, indeed, Apotex is not arguing that the period of time from February 8 onward is part of its laches argument. (See tr. at 115.)

The parties continued to negotiate throughout the spring, reducing their agreements to written form in the successive March 17, 2006 and May 26, 2006 agreements. Both of these agreements contained provisions that Apotex would not launch its generic product and Sanofi would not move for a temporary restraining order or a preliminary injunction during the regulatory review period. (See Mar. 17, 2006 Agreement at ¶ 19; Second Agreement at ¶ 15.) Sanofi then moved for a preliminary injunction on August 15, 2006, five business days after Sanofi’s launch on August 8, 2006, on the earliest date it was permitted to so move pursuant to the Second Agreement. Because active negotiations between the parties is a legitimate excuse to a delay in bringing suit sufficient to bar a laches defense, A.C. Auckerman, 960 F.2d at 1033, the

Court finds that Sanofi did not unreasonably or inexcusably delay its motion for a preliminary injunction.

Finally, the Second Agreement expressly barred Sanofi from seeking a temporary restraining order or a preliminary injunction until 5 business days *after* Apotex's launch, (Second Agreement at ¶ 15(i)), and anticipated that Sanofi would move for a preliminary injunction if Apotex did launch, setting forth that Sanofi "will not file for a preliminary injunction until Sanofi gives Apotex 5 business days notice . . . of its intention to do so, which notice will not be given before Apotex has initiated a launch of a generic clopidogrel product." (Second Agreement at ¶ 15(ii).) Apotex cannot now claim that Sanofi caused Apotex material prejudice by waiting until after Apotex's launch to bring a motion for preliminary injunction.

In sum, the defense of laches is inapplicable in the circumstances of this action.

#### **B. Unclean Hands**

The Court similarly rejects Apotex's "unclean hands" defense. Apotex alleges that Sanofi has approached the Court with "unclean hands" based on allegedly false statements Sanofi made to regulators when Sanofi presented the Second Agreement for regulatory approval. Invoking the hoary and valid equitable principle that "he who seeks equity must do equity," Koster v. Lumbermens Mut. Cas. Co., 330 U.S. 518, 522 (1947), Apotex requests that the Court deny Sanofi's motion for a preliminary injunction. However, the legal authority Apotex cites is inapposite. In the cases relied upon by Apotex, equitable relief was denied when parties had committed perjury before the PTO, or litigation misconduct or fraud on the court, rather than alleged wrongdoing during the course of settlement negotiations. See e.g., Precision Instrument Mfg. Co. v. Auto Maint.

Mach. Co., 324 U.S. 806 (1945) (patent obtained by perjury); Hazel-Atlas Glass Co. v. Hartford-Empire Co., 322 U.S. 238 (1944) (same); Keystone Driller Co v. Gen Excavator Co., 290 U.S. 240 (1933) (fraud on the court); Aptix Corp. v. Quickturn Design Sys., Inc., 269 F.3d 1369, 1374 (Fed. Cir. 2001) (litigation misconduct). The conduct of the parties during settlement negotiations does not affect the validity of the patent or the veracity of submissions to this Court, and therefore has no relevance to the question of whether a preliminary injunction should issue. The Court will not consider a dispute regarding the conduct of settlement negotiations in the context of this motion for preliminary relief.

## **V. REMEDY**

### **A. Injunction**

Sanofi's motion seeks an order both enjoining Apotex from infringing the '265 patent and recalling all of the generic product manufactured and distributed since the August 8, 2006 launch by Apotex. Because all four of the requisite factors weigh in favor of a preliminary injunction, Sanofi's motion is granted to the extent that Apotex is enjoined from engaging in any activity that infringes U.S. Patent No. 4,847,265, pending a final decision on the merits of this action. The trial of this action shall commence on January 22, 2007.

The motion is denied to the extent it seeks a recall of the generic product already manufactured and distributed. Although "it is well settled that a court has the power to issue a mandatory injunction to restore the situation to the status quo when a party, with notice of impending injunction proceedings, completes or performs the action sought to be enjoined," F. Alderete General Contractors, Inc. v. United States, 715 F.2d 1476,

1480 (Fed. Cir. 1983), this is not a case where the unusual remedy of a mandatory injunction ordering a product recall is appropriate. Here, Sanofi specifically foresaw the possibility that Apotex would declare that there had been Regulatory Denial as defined in the agreement (see Second Agreement at ¶ 13), and that Apotex would then be able to launch its generic. Sanofi also agreed that it would “not seek a temporary restraining order or preliminary injunction” for 5 business days after Regulatory Denial became effective (Second Agreement at ¶ 15(i)) and indeed, even after that 5 day period expired, Sanofi would not file for a preliminary injunction until it had given Apotex 5 business days notice “of its intention to do so,” and that notice “will not be given before Apotex has initiated a launch of a generic clopidogrel product.” (Second Agreement at ¶ 15(ii).) In that same agreement, Sanofi also agreed not to launch its own generic clopidogrel product before a launch by Apotex of a generic clopidogrel product. (See Second Agreement at p 15(ii).) These provisions all foresaw the possibility that Apotex would launch a generic product and prohibited Sanofi from seeking injunctive relief for a specific period of time after the launch occurred. Thus, Sanofi participated in a knowing business decision, in exchange for which it received valuable consideration (see, e.g., Second Agreement at pp3, 49), to face a market situation whereby Apotex had launched its generic product into the marketplace and Sanofi agreed not to seek an injunction for a limited period of time during which Apotex concededly was permitted to sell its generic. Under these circumstances, a mandatory injunction ordering recall would be inequitable and the Court will not intervene to reverse the effects of Sanofi’s own agreement. See Abbott Labs., 452 F.3d at 1349; Hughes Tool Co., 718 F.2d at 1578.



## **B. Bond**

Rule 65(c) of the Federal Rules of Civil Procedure provides that no “preliminary injunction shall issue except upon the giving of security by the applicant, in such sum as the court deems proper, for the payment of such costs and damages as may be incurred or suffered by any party who is found to have been wrongfully enjoined or restrained.”

Although this Court has found no authority from the Federal Circuit governing the parameters for the amount of the bond—and the parties have supplied none—the Second Circuit has clarified that “Rule 65(c) gives the district court wide discretion to set the amount of a bond.” Corning Inc. v. PicVue Elecs., Ltd., 365 F.3d 156, 158 (2d Cir. 2004) (quoting Doctor’s Assocs., Inc. v. Distajo, 107 F.3d 126, 136 (2d Cir. 1997)); see also Ferguson v. Tabah, 288 F.2d 665, 675 (2d Cir. 1961) (“the matter of a bond is for the discretion of the trial court”).

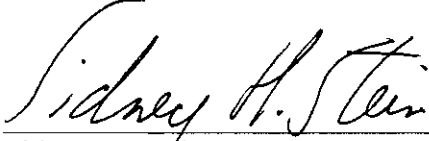
Considering the information provided by the parties during the preliminary injunction hearing and in the affidavits of Dr. Bernard Sherman dated August 16, 2006, Sandra L. Cartie dated August 22, 2006, and Dr. Frank Bernatowicz dated August 24, 2006, and the estimates by the parties of Apotex’s potential lost profits, lost market share and associated costs of relaunch in the event Apotex is found “to have been wrongfully enjoined or restrained,” Fed. R. Civ. P. 65(c), the Court sets the amount of the bond at \$400 million.

## **VI. CONCLUSION**

Because the four relevant factors set forth by the Federal Circuit weigh in favor of the grant of a preliminary injunction and Apotex’s equitable defenses to an injunction are without merit, Sanofi’s motion is granted to the extent that Apotex shall be enjoined from

infringing Sanofi's '265 patent during the pendency of this action. Sanofi shall post a bond pursuant to Fed. R. Civ. P. 65(c) in the amount of \$400 million.

Dated: New York, New York  
August 31, 2005

  
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Sidney H. Stein, U.S.D.J.